ACTIVITY PROFILE OF PIRACETAM IN PSYCHOSYNDROMES AND SYMPTOMATIC PSYCHOSES

A. Voelkel

Translation of "Über das Wirkungsprofil von Piracetam bei Psychosyndromen und symptomatischen Psychosen," Arzneimittel-Forschung (Drug Research), Vol. 24, No. 8, 1971, pp. 1127-1129

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16. Abstract The encephalotropic effect of 2-oxo-pyrrolidine-acetamide (Piracetam) is observed in patients with different reversible encephalopathic psychosyndromes combined with depressive or paranoid syndromes. This pilot study shows that the most important effect is a remarkable restoration of memory, vigilance, lucidity, and differentiation. Furthermore, Piracetam is able to provoke psychotic reactions with paranoid symptoms and hallucinations in cases with uncertain subclinical psychotic syndromes with dissimulation.

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ACTIVITY PROFILE OF PIRACETAM[1] IN PSYCHOSYNDROMES AND SYMPTOMATIC PSYCHOSES

A. Voelkel

Piracetam is 2-oxo-pyrrolidine-acetamide and is derived /1* chemically from the neurotransmitter and neuromodulator γ-amino-butyric acid. Synthesized in 1963, Piracetam has been marketed in France and Belgium since 1972, and in Switzerland since 1974. Registration here is expected in 1974.

Pharmacologically, Piracetam first attracted attention because of its inhibiting effect on central nystagmus, i.e. that triggered by stimulation of the Corpora genic. later., and on vestibular nystagmus. Further studies discovered a protective effect against pharmacogenic O_2 deficiency in the brain as well as a shortening of the post-anoxic recovery time. Also, improved learning results were found in labyrinth tests and other tests. These and other pharmacological studies suggested possible activation of telencephalic structures. Even in high dosages, Piracetam has no toxic, sedative, stimulant, or neuroleptic effects; it also behaves indifferently in cardiovascular and respiratory tests, and does not affect cerebral circulation parameters, nor /2 does it affect cholinergic, adrenergic, histaminergic, and seratoninergic receptors. It is eliminated almost entirely by the kidneys, without being metabolized; its half-time in the blood is about 4.5 hours in human beings. Biochemical studies suggest that it exerts an activating influence on the energy-producing system of the cerebral cell, and intervenes in RNA synthesis.

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[1] Marketed under the names NORMABRAIN, Cassella-Riedel Pharma GmbH, Frankfurt am Main, and NOOTROP, UCB-Chemie, Sindorf.

* Numbers in the margin indicate pagination in the foreign text.

In line with the special nature of our clinic, which conducts emergency and preliminary psychiatry, we have used this agent in:

1. diffuse cerebral and mnesic psychosyndromes with/ /without psuedoneurasthenic, affective, or paranoid-hallucinatory accompanying symptoms in cerebral-atrophic changes demonstrated by encephalograms after insufflation of air into cerebral sinuses (12 patients),

2. organic psychoses resulting from predominantly chronic intoxications due to alcohol, bromine, barbiturates, or psychoactive pharmaceuticals, or from polyvalent drug abuse (21 patients),

3. diffuse cerebral and mnesic psychosyndromes in combination with depressive moods and/or manic productivity in arteriosclerosis of the cerebrum with and without focal brain lesions, and in isolated cases following cerebral trauma (13 patients),

4. chronic cyclothymias with increasingly cerebral-organic coloration in presenility/senility and in late cyclothymias complicated by involutional aging processes (6 patients),

5. lastly, Piracetam has been used in differential diagnosis to provoke symptoms in masked productive diseases, by analogy with the procedure of Heinrich and Petrilowitsch [1] with the MAO inhibitor serine hydrazide [2] (8 patients).

As for the methods of treatment, we refer to the following discussion of the various therapy groups. Important factors in assessing psychopathological syndromes are not only the pattern of symptoms, but also the conditions under which these symptoms show up and the times at which they do so, broken down by acuteness,

duration, and reversibility. A significant factor on the syndrome-genetic level is the individual disposition, including pharmaco-therapeutic susceptibility. Furthermore, the very diverse "morbo-genic" factors recently pointed out by Helmchen and Hippius [3] should be taken into account; as well as the summation of disease-provoking situational and peristatic factors. However, in more than 10,000 cases histories, Peters and Gille [4] found 5.5% acute psychoses with physical causes, the main causes being alcohol and /3
cerebrovascular processes in about 70% of the cases. These points may adequately explain why no statistical analysis was undertaken as a part of this pilot study in view of the relatively small number of about 60 observations, and also why no double-blind control was instituted.

We administered Piracetam orally in capsules containing up to 400 mg, and up to 4.0 g daily intramuscularly and as a continuous intravenous drip for an average duration of 3 weeks, without any other encephalotropic substances being administered at the same time.

1. In the first therapy group with diffuse cerebral and mnesic psychosyndromes together with pseudoneurasthenic history, affective disturbances, or paranoid symptoms, the patients exhibited conditions which had been described in 1951 by Bronisch [5] and also by Kehrer [6] as cerebral-atrophic processes in middle age, and in 1955 by Beringer and Mallison [7] as premature failure symptoms. Encephalography with insufflation of air carried out for diagnostic reasons showed changes such as a moderate hydrocephalus int. et ext. as well as an increase in β-globulin in the cerebrospinal fluid in most of the cases [8], often in connection with a slightly elevated cell count in the fluid.

As early as the fifth day of treatment in the therapy with Piracetam showed marked improvements in lucidity, vigilance,

concentration, and communication, as well as in -- tested in individual cases by a simple learning experiment -- the learning time upon brief exposure [9], the precision of a word determined by context and situation [10], and competence in verbal communication [11]. The initial conceptual deficit [12] diminished visibly, the disproportion between perception of self and reality was reduced, and behavior consistent with the situation was restored. If these effects were not found by the fifth to seventh day of therapy, prolonged therapy usually proved fruitless as well in our observations. The therapeutically relevant effects on verbal activity and verbal competence were not observed unless the cerebrotrophic changes determined in the pneumoencephalogram were relatively small, although accompanied by pronounced mnesic and psychopathological syndromes. The effects of Piracetam therapy were rather indistinct in the affective area (relief phenomenon?) and were not found at all in paranoid disturbances of thought content; however, these psychotic symptoms could be treated concomitantly by thymoleptic or neuroleptic methods without incompatibility manifestations.

2. Delirious symptoms after alcohol withdrawal passed very rapidly. Under Piracetam therapy, the patients are lucid, responsive, communicative, and not pharmacogenically confused, drowsy, or slowed as in the otherwise common therapy with Clomethiazol. On the other hand, vegetative withdrawal symptoms are not appreciably affected, and disturbances of sleep and psychomotor restlessness appear enhanced [13]. No noteworthy influence was observed on the post-delirium memory deficiency, which, combined with losses in critical faculties and judgment, can make up the main part of the irreversible defect syndrome in the sense of a persistent personality change, a local cerebral psychosyndrome, or a Korsakoff's Syndrome. /4

3. The psycho-organic psychopathological mixed syndromes in usually combined chronic medication abuse (bromine, barbiturates,

phenacetin) appear very similar to those after the alcohol-withdrawal delirium, but are more prolonged and periodic. Abuse usually begins at an unspecified time, and the family physician and social environment are not well acquainted with duration and extent [14]. We must anticipate late and echo deliria, particularly in bromism [15], and spontaneous epileptic seizures in rarer cases, through about the 24th day of abstinence. Piracetam therapy obviously shortens this risk period, and we no longer observed any echo deliria or cerebral convulsions; the duration of limited lucidity, intellectual performance, and communication likewise appeared shortened. The renal elimination time for toxogenic drugs is not reduced, as chemical urine analyses (Inst. of Forensic Medicine of the FU) have demonstrated. The duration of the pharmacogenic-toxic beta rhythm in the EEG is not decreased. In several cases of post-suicidal or iatrogenic psychoactive drug overdoses (Haloperidol, Doxepin, Perphenazin, Perazin), we observed quite similar sequences of events; Piracetam can relieve the mnesic psychosyndrome in a short time in these intoxications as well, and can relatively rapidly restore lucidity and vigilance.

4. Youthful drug patients with mixed paranoid-hallucinatory or depressive-dysphoric symptoms, often enough combined with delirious features, create diagnostic problems for the psychiatrist, particularly since a psychotic disease behind the drug-induced cerebral-organic psychopathological mixed syndrome must be either ruled out or treated. In these cases, Piracetam does not influence the anxious excitation, psychomotor restlessness, sleep disturbances, or cerebral-organic symptoms. This polymorphic syndrome with alternating lucidity, disorientation, confabulation, gloominess, and paranoid-hallucinatory symptoms was appreciably relieved during infusion Piracetam therapy for several hours past /5
the infusion period only in two youthful patients. At the same time, verbal expression and competence behavior was temporarily improved [16a-c]. In neither of these patients were any symptoms of schizophrenic psychosis subsequently observed. In three other

youthful patients with corresponding mixed symptoms, the administration of Piracetam had no effect; in these patients, the initial exogenous-endogenous mixed syndrome gradually became a persistent paranoid-hallucinatory set of symptoms, which must be considered a chronic psychosis of the schizophrenic pattern.

It may be that application of Piracetam may make it possible to distinguish endogenous psychoses from seemingly endogenous but actually pharmacogenic-toxic psychoses at an early date.

5. We obtained no success in Piracetam therapy for diffuse cerebral and mnesic psychosyndromes in cerebrovascular processes in the sense of a hemodynamic insufficiency with marked general sclerotic symptoms, chronic hypertonia, intermittent ischemias, and apoplectic resulting states with focal and tool disturbances. Instead, there seemed to be an increase in the existing symptoms (premature fatigue, depression, affective incontinence, loss of memory, weakness in critical faculties, neurological microsymptoms progressing in small steps, indistinct speech, mimic weakness, and certainly psychomotor restlessness as well as trouble in falling and staying asleep).

6. On the other hand, rather prompt response to Piracetam therapy is observed in cerebrosclerotic patients with predominantly cerebral-parenchymatous disturbances with no symptoms of hemodynamic insufficiency, but with loss of memory, verbosity, perseveration, unclear and ambiguous statements, fussiness, uncertainty, and general timidity. Vocabulary is improved, content is less insignificant and more cohesive, awareness of surroundings is improved, nervousness in the face of demands decreases, demands for activity fall away with time, powers of communication increase, and risk behavior in relation to cognitive features is less indeterminate [17].

7. A further treatment group includes cyclothymic patients in presenility/senility with disease durations between 17 and 24 years and ages between 65 and 77, exhibiting losses of memory and late cyclothymias, as Glatzel [18] has again recently described, which likewise attract attention by involution-related losses of memory. In both forms of the disease, therapy with Piracetam results in an appreciable regression of these peripheral cerebro-organic phenomena. In all cases, there were no complications in the accompanying thymoleptic treatment with Amitryptilin or, in the case of a manic episode, with the carboanhydrase inhibitor acetazolamide or Sultiam [19]. /6

8. In conclusion, we should mention two effects induced by Piracetam which surprised us at first. Paranoid motivation caused a 43-year-old patient to feign a traumatic loss of cerebral function. He received Piracetam, whereupon distinct paranoid-hallucinatory symptoms appeared after a few days, revealing the underlying psychotic syndrome. In the end, successful neuroleptic therapy was introduced. Because of this incident, we occasionally and successfully administered Piracetam for differential-diagnostic and differential-typological purposes; it appears that Piracetam is at least as good as the other MAO inhibitors used in these cases, without involving the same risks.

Another side effect of Piracetam, this time an undesirable one, is that depressive-suicidal reactions can appear in cerebro-organic psychosyndromes or functional psychoses, if application of Piracetam increase self-examination, self-criticism, and introspection to such an extent that a near-realistic estimate of the existing weakness of cerebral function or depression of the personality level is made. Such a depressive reaction was accompanied by suicidal tendencies in a patient with alcohol-induced Korsakoff's Syndrome, until Piracetam was discontinued.

Summary

2-oxo-pyrrolidine-acetamide (Piracetam) increases vigilance and lucidity, and has reintegrating and deleveling therapeutic effects in reversible diffuse cerebral and mnesic psychosyndromes of various origins, as long as these syndromes are based primarily on a cerebral-parenchymatous disturbance, and not on a primary cerebrovascular disease. In subclinical psychotic disease, Piracetam provokes symptoms, and can thus assist in differential diagnosis.

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